subject. Claims 69-96 are directed to a method of treating a malignant tumor in a human subject. Claims 97-107 relate to a pharmaceutical composition. Claims 108-109 are directed to a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor.

REMARKS

The Office Action and Applicant's Response

No claims were allowed.

The Examiner noted the telephonic restriction requirement of May 30, 2000, in which two groups were presented to Applicant:

Group I, Claims 1-34 and 97-109 drawn to a method of delivering a medicant to an abnormal brain region in a mammalian subject; to a pharmaceutical composition; and to a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor; and

Group II, Claims 35-109, drawn to a method of delivering a medicant to a malignant tumor in a mammalian subject; to a method of treating a malignant tumor in a human ubject; and to a pharmaceutical composition; and to a kit for enhancing the delivery of a medicant to an abnormal brain region and/or to a malignant tumor.

The Examiner directed Applicant to amend Claims 97-109 to read on the elected group.

The Examiner acknowledged Applicant's provisional telephonic election of Group I, made on May 31, 2000. Applicant confirms this election without traverse of Group I (Claims 1-34 and 97-109). Applicant has herein canceled Claims 35-96 as being directed to an unelected group and has amended Claims 101, 104, and 108 in accordance with Applicant's election, as the Examiner directed.

A. Rejection of Claims 1-34 and 97-109 under 35 U.S.C. § 103(a)

Claims 1-34 and 97-109 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Black (U.S. Patent No. 5,434,137), in view of the combination of Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947) for the following reasons:

> **Black (U.S. Patent No. 5,434,137) teaches (specification and claims 1-6) a method for selectively opening abnormal brain tissue capillaries of a mammal in order to allow selective passage of neuropharmaceutical agents into abnormal brain tissue. The method uses infusion of bradykinin into the carotid artery. The reference further teaches that bradykinin selectively opens abnormal brain tissue capillaries without opening normal brain capillaries and that the invention can be used for brain tumors and abnormal tissue resulting from ischemia, multiple sclerosis, cerebral abscess, and any number of different diseases. The reference further teaches that any number of the multitude of well-known neuropharmaceutical agents and/or diagnostic agents can be used. The reference further teaches a pharmaceutical formulation of the aforementioned method, in any of the well-known pharmaceutical carriers, including 0.9% saline. The reference fails to teach that bradykinin is a potassium channel agonist or that it increases potassium flux.**
>
> **Sobey, et al. teaches vasodilator responses of cerebral artierioles to bradykinin involve the activation of potassium channels, thus increasing potassium flux and potassium concentrations.**
>
> **Additionally, activators/agonists of potassium channels were well known in the art at the time of filing. For example, Cherksey teaches (page 4) a multitude of potassium channel agonists, including, RP52891, cromakalim, lemakalim, celikalim, R0316930, 507-PCO-400, HOE-234, minoxidil, diazoxide, pinacidil and nicorandil.**
>
> **Therefore, in view of such, it would have been obvious for one of ordinary skill in the art to determine that the action of allowing selective passage of neuroharmaceutical agents into abnormal brain tissue, as taught by Black, is based on the activation of potassium channels, as taught by Sobey, et al.. It would have been further obvious for one skilled in the art to utilize other potassium channel activators, or agonist, as taught by Cherksey, to achieve the same effect taught by Black. One would have been motivated to do so in order to provide for the benefit of selectively treating abnormal brain regions, as taught by Black, using potassium channel agonists other than bradykinin that may provide for better membrane permeability and/or potassium channel activation in certain abnormal brain region states and thus better drug delivery efficacy.**

To establish a prima facie case of obviousness, each of three criteria must be met. (MPEP 2143). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)(citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 [Fed. Cir. 1988]). Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. *In re Royka and Martin*, 490 F.2d 981, 180 USPQ 580, 583 (CCPA 1974).

Applicant disagrees that the cited combination of Black, Sobey *et al.*, and Cherksey references make the claimed invention obvious, because (1) neither the cited references nor the

general knowledge in the art at the time the present application was filed suggested modifying the method of Black to obtain the claimed method; (2) minus the disclosures of the specification as filed, there would not have been a reasonable expectation of success for the claimed method and compositions; and (3) the cited references failed to suggest all the present claim limitations.

(1) The cited Sobey *et al.* and Cherksey references and the general knowledge in the art failed to suggest modifying the method of Black to obtain the claimed method.

The claimed invention is directed to a method of delivering a medicant to an abnormal brain region in a mammalian subject, which method involves "administering to a mammalian subject having an abnormal brain region a potassium channel agonist, other than bradykinin or a bradykinin analog, under conditions and in an amount sufficient to increase the permeability to the medicant of a capillary or arteriole delivering blood to cells of the abnormal brain region" (e.g., Claim 1 and Claims 2-17 dependent therefrom). Claim 18 also recites that the potassium channel agonist is administered ". . . under conditions and in an amount sufficient to increase potassium flux through a calcium-activated or ATP-sensitive potassium channel in an endothelial cell membrane of a capillary or arteriole delivering blood to cells of the abnormal brain region, whereby the capillary or arteriole is made more permeable to the medicant." In addition, the method includes the step of "administering to the subject simultaneously or substantially simultaneously with the potassium channel agonist the medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions." (E.g., Claims 1 and 18, and Claims 2-17 and 19-34 dependent therefrom).

The claimed invention is also directed to a pharmaceutical composition comprising "a combination of a potassium channel agaonist other than bradykinin or a bradykinin analog, formulated . . . together with a medicant" (E.g., Claims 97-107), and to a kit comprising a potassium channel agonist, *other than* bradykinin or a bradykinin analog, and instructions for using the potassium channel agonist for enhancing delivery of a medicant to an abnormal brain region (e.g., Claims 108-109).

In contrast, the cited Black patent taught the use of bradykinin or a bradykinin analog for introducing a neuropharmaceutical or neurodiagnostic agent into abnormal brain tissue present in a mammal (e.g., Claim 1 of Black patent). Black taught that bradykinin and its analogs could selectively increase the permeability of abnormal brain tissue capillaries to both low and high molecular weight neuropharmaceutical agents (e.g., column 1, line 65 through column 2, line 2), but, as noted by the Examiner, Black failed to teach that bradykinin and its analogs are potassium channel agonists. Moreover, Applicant is unaware of any reference known in the art at the time the present specification was filed that described such properties of bradykinin or its analogs. Also, Black failed to describe a mechanism for bradykinin-induced permeability increase in abnormal capillaries, and minus the hindsight provided by the disclosures of the present specification, the involvement of calcium-activated potassium channels (K_{Ca}) or ATP-sensitive potassium channels (K_{ATP}) in increasing permeability of abnormal brain microvasculature, in vivo, was unknown in the art.

The Sobey *et al.* reference also failed to teach the involvement of calcium-activated or ATP-sensitive potassium channels in increasing permeability of the microvasculature in abnormal brain regions. As noted by the Examiner, Sobey *et al.* taught the involvement of calcium-activated potassium channels in the *vasodilatation* of brain capillaries, but failed to describe any effect on micro*vascular permeability*. Similarly, Cherksey described a class of chemicals with potassium channel-activating properties, which Cherksey taught were useful for treating hypertension, addiction, asthma, incontinence, and other conditions presumably related to vascular hypertension. (See, e.g., Abstract, column 4, lines 6-27). Cherksey taught that the opening of vascular plasmalemmal potassium (K^+) channels produces loss of cytosolic K^+, resulting in "cellular hyperpolarization and functional *vasorelaxation*." (Column 3, line 59 through column 4, line 5; emphasis added), but Cherksey failed to teach any connection with microvascular permeability.

The teachings of Sobey *et al.* and Cherksey concerning potassium channels and associated vasodilatation/vasorelaxation would not have suggested to one of skill in the art that calcium-activated or ATP-sensitive potassium channels could also affect microvascular permeability, because vasodilatation and microvascular permeability are two different

physiological responses of the microvessels to vasoactive compounds. Applicant is unaware of any references available at the time the present specification was originally filed that linked vasodilatation to the permeability of abnormal brain capillaries, in vivo. Therefore, Sobey *et al.*, Cherksey, and the general knowledge in the art failed to suggest or provide motivation to the skilled artisan to modify the method of Black by instead administering "a potassium channel agonist, other than bradykinin or a bradykinin analog, to a subject simultaneously or substantially simultaneously" with the administration of a medicant, so that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions, as recited, e.g., in Claims 1 and 18.

(2) Minus the disclosures of the specification as filed, there would not have been a reasonable expectation of success for the claimed method and compositions.

Minus the disclosures of the specification as filed, there would not have been a reasonable expectation of success for the claimed method and compositions, because the skilled artisan was aware that a state of *vasodilation* or *vasorelaxtion* does not necessarily correlate with an increase in the permeability of abnormal capillaries. For example, leukotriene C4 (LTC4) is a well known *vasoconstrictor*, which has also been shown to increase microvascular permeability in abnormal brain capillaries. (See, e.g., *Yakubu, M. A. et al., Hematoma-induced enhanced cerebral vasoconstrictions to leukotriene C4 and endothelin-1 in piglets: role of prostanoids*, Pediatr. Res 38(1):119-23 [1995], abstract appended as Exhibit A; and Black *et al.*, *Selective opening of the blood-tumor barrier by intracarotid infusion of leukotriene C_4*, J. Neurosurg. 72:912-16 [1990], appended as Exhibit B).

Success for the claimed method, which employs either calcium-activated potassium channels or ATP-sensitive potassium channels (e.g., Claim 18), would also not be expected because these were known in the art to be chemically distinct with respect to vasodilatory properties. For example, vasodilatation mediated by bradykinin was shown not to be inhibited by glibenclamide, a specific inhibitor of ATP-sensitive potassium channels, while vasodilatation mediated by prostacyclin or cromakalim was shown to be inhibited by glibenclamide; conversely, inhibitors of bradykinin-mediated vasodilatation, such as L-NAME

or L-NNA, were shown not to inhibit vasodilatation mediated by cromakalim. (See, e.g., Jackson, W.F. *et al.*, *Prostacyclin-induced vasodilatation in rabbit heart is mediated by ATP-sensitive potassium channels*, Am. J. Physiol. 264(1 Pt 2):H238-43 [1993], abstract appended as Exhibit D; Liu, Q. and Flavahan N.A., *Hypoxic dilatation of porcine small coronary arteries: role of endothelium and KATP-channels*, Br. J. Pharmacol. 120(4):728-34 [1997], abstract appended as Exhibit E; and Herrera, G.M. *et al.*, *Maintained vasodilatory response to cromakalim after inhibition of nitric oxide sysnthesis*, J. Cardiovasc. Pharmacol. 31(6):921-29 [1998], abstract appended as Exhibit F). Therefore, the mechanism of vasodilatory action of bradykinin was thought to be independent of the pathway mediated by ATP-sensitive potassium channels. Consequently, success would not have been expected for the claimed method that employs an agonist of either calcium-activated potassium channels or ATP-sensitive potassium channels, as recited in Claim18.

In addition, there are other pathways that are clearly unrelated to vasodilatation, by which vascular permeability was known to be affected. For example, a number of calcium channel antagonists that are not known to increase vasodilatation of cerebral microvessels have been shown to increase the permeability of abnormal brain capillaries. (See, Matsukado *et al.*, *Selective increase in blood-tumor barrier permeability by calcium antagonists in transplanted rat brain tumors*, Acta Neurochir. Suppl. (Wien) 60:403-05 [1994], abstract appended as Exhibit C).

Further, all of the cited references and the general knowledge in the art failed to teach that the relative quantity of potassium channels in abnormal microvasculature is greater compared to the quantity in normal microvasculature. This feature contributes to the successful functioning of the claimed method of delivering a medicant to an abnormal brain region in a mammalian subject. It is only the present specification that provides this knowledge (e.g., in Example 2).

Therefore, minus the hindsight provided by the disclosures of the present specification, success would not have been reasonably expected for the claimed method of delivering a medicant to an abnormal brain region in a mammalian subject, employing potassium channel agonists. Given this, the successful utility of the pharmaceutical compositions and kits

(Claims 97-109) would also not have been reasonably expected based on the cited Black, Sobey *et al.*, and Cherksey references.

(3) The Black, Sobey *et al.*, and Cherksey references failed to suggest all the claim limitations.

The Black, Sobey *et al.*, and Cherksey references, cited by the Examiner, failed to suggest all the claim limitations of Claims 1-34 and 97-109. For example, as discussed above, the Black, Sobey *et al.*, and Cherksey references, combined with the general knowledge in the art, failed to teach a connection between the permeability of brain microvasculature and potassium channels. Consequently, the references failed to suggest "administering to a mammalian subject having an abnormal brain region *a potassium channel agonist, other than bradykinin or a bradykinin analog*" in conjunction with "administering to the subject simultaneously or substantially simultaneously with the potassium channel agonist [a] medicant," as recited in Claim 1 and in Claims 2-17, directly or indirectly dependent therefrom.

Since the cited references failed to teach a connection between vascular permeability and potassium channels, they also failed to suggest the limitation of administering the potassium channel agonist "under conditions and in an amount sufficient to increase potassium flux through *a calcium-activated or ATP-sensitive potassium channel*," as recited in Claim 18 and in Claims 19-34, directly or indirectly dependent therefrom.

By failing to teach a connection between the permeability of brain microvasculature and potassium channels, the cited references failed to suggest "a pharmaceutical composition comprising a *combination* of a *potassium channel agonist, other than bradykinin or a bradykinin analog*, formulated in a pharmaceutically acceptable solution *together with a medicant*," as recited in Claim 97, and in Claims 98-107, directly or indirectly dependent therefrom.

By failing to teach a connection between the permeability of brain microvasculature and potassium channels, the cited references failed to suggest "a kit for enhancing the delivery of a medicant to an abnormal brain region, comprising: *a potassium channel agonist, other than bradykinin or a bradykinin analog; and instructions for using the potassium channel*

agonist for enhancing the delivery of a medicant," as recited in Claim 108 and in Claim 109, dependent therefrom.

Finally, the cited references and the general knowledge in the art also failed to teach that the relative quantity of potassium channels in abnormal microvasculature is greater compared to the quantity in normal microvasculature. Consequently, they failed to suggest the limitation "that the medicant is delivered selectively to the cells of the abnormal brain region compared to normal brain regions," as recited directly or indircetly in Claims 1-34.

Thus, Black, Sobey *et al.*, and Cherksey failed to suggest all the limitations in Claims 1-34 and 97-109.

Therefore, Applicant respectfully asserts that the Examiner has not met his burden in asserting prima facie obviousness, based on the combination of Black, Sobey *et al.*, and Cherksey, and requests the Examiner to withdraw the rejection of Claims 1-34 and 97-109 over the cited references, under 35 U.S.C. §103(a).

B. Rejection of Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 under the Doctrine of Obviousness Type Double Patenting

The Examiner rejected Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 under the Doctrine of Obviousness Type Double Patenting over Claims 1-6 of Black (U.S. Patent No. 5,434,137), in view of Sobey *et al.* (Stroke 28[11]:2290-4 [1997]) and Cherksey (U.S. Patent No. 5,234,947). The examiner stated that this rejection could be overcome by a terminal disclaimer, if the cited Black patent and the above-referenced application are both owned by the Medical Center. The Examiner stated the following reasons for the rejection:

> **The teachings of Sobey, et al. and Cherksey have been described in paragraphs 11 and 12, respectively, of the instant office action.**
>
> **Therefore, in view of such, it would have been obvious for one of ordinary skill in the art to determine that the action of allowing selective passage of neuropharmaceutical agents into abnormal brain tissue, as taught by Black, is based on the activation of potassium channels, as taught by Sobey, et al.. It would have been further obvious for one skilled in the art to utilize other potassium channel activators, or agonist, as taught by Cherksey, to achieve the same effect taught by Black. One would have been motivated to do so in order to provide for the benefit of selectively treating abnormal brain regions, as taught by Black, using potassium channel agonists other than bradykinin that may provide for better membrane permeability and/or potassium channel activation in certain abnormal brain region states and thus better drug delivery**

efficacy.

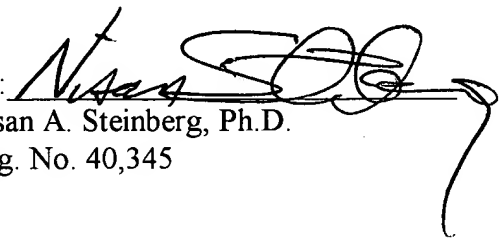
Applicant disagrees that the combination of the cited Black, Sobey *et al.*, and Cherksey references makes obvious the invention claimed in Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34, because these three cited references failed to make obvious any of Claims 1-34, as discussed in detail above.

Therefore, the rejection based on the doctrine of obviousness type double patenting is improper, and Applicant respectfully requests the Examiner to withdraw the rejection of Claims 1-5, 7-9, 11, 12, 14-22, 24-26, and 28-34 on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,
SIDLEY & AUSTIN

By: 
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